

The Chinese University of Hong Kong

Department of microbiology
Joint Graduate Seminar 2010

Oncogenic viruses and human cancer

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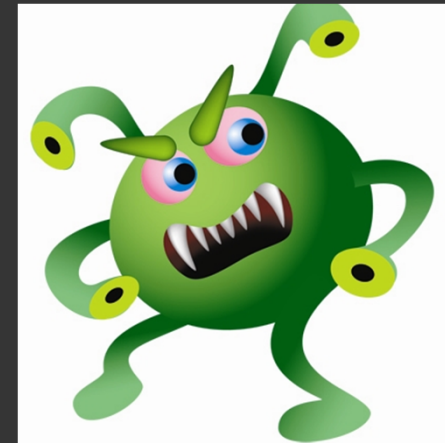
Content

① Global cancer statistics

② Viral oncology

- ◆ Features of viral oncogenesis
- ◆ Tumor-associated viruses
- ◆ Viral transformation and mechanisms

③ Cervical cancer



1. Global cancer statistics

◎ 2008

- > 12.7 million new cases
- > 7.6 million cancer deaths

◎ 2030

- > Estimate 21.4 million new cases
- > Estimate 13.2 million cancer deaths

◎ 15-20% human cancers associated with oncogenic viruses



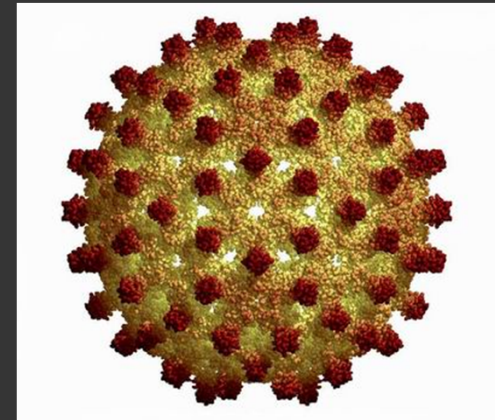
2. General features of Viral Oncogenesis

- ⊙ transform host cells conferring neoplasia
- ⊙ Not the sole factor,
 - > host immunity
 - > host genetic mutation
 - > chronic inflammation, etc
- ⊙ Small proportion of infected persons develop cancer

Tumor-associated viruses

◎ 6 well-known DNA/RNA tumor virus

- > Epstein-Barr virus (EBV) 人類疱疹病毒第四型
- > Hepatitis B virus (HBV) 乙型肝炎病毒
- > Human papillomavirus (HPV) 人類乳頭瘤病毒
- > Kaposi sarcoma associated herpesvirus (KSHV) 人類疱疹病毒第八型
- > Hepatitis C virus (HCV) 丙型肝炎病毒
- > Human T-cell lymphotropic virus type 1 (HTLV-1) 人類T淋巴細胞病毒I型



Viral transformation

1. Carry viral oncogenes (v-oncs)

> Stimulatory for cell growth e.g.

- Growth factor
- Signal transduction protein
- Transcription factors

2. Alter expression of tumor-suppressor genes

> Inhibitory for cell growth e.g.

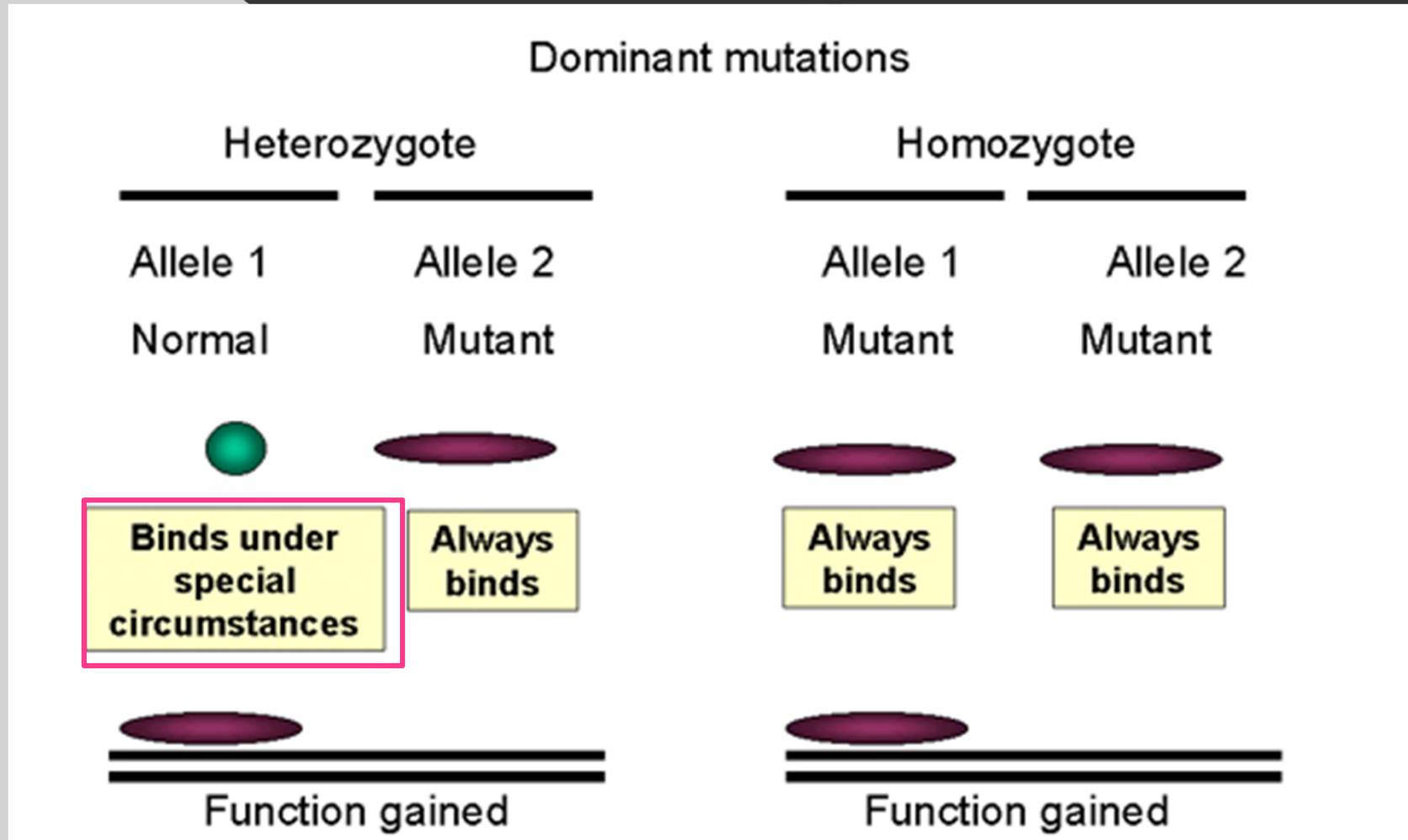
- Retinoblastoma
- p53

Viral transformation

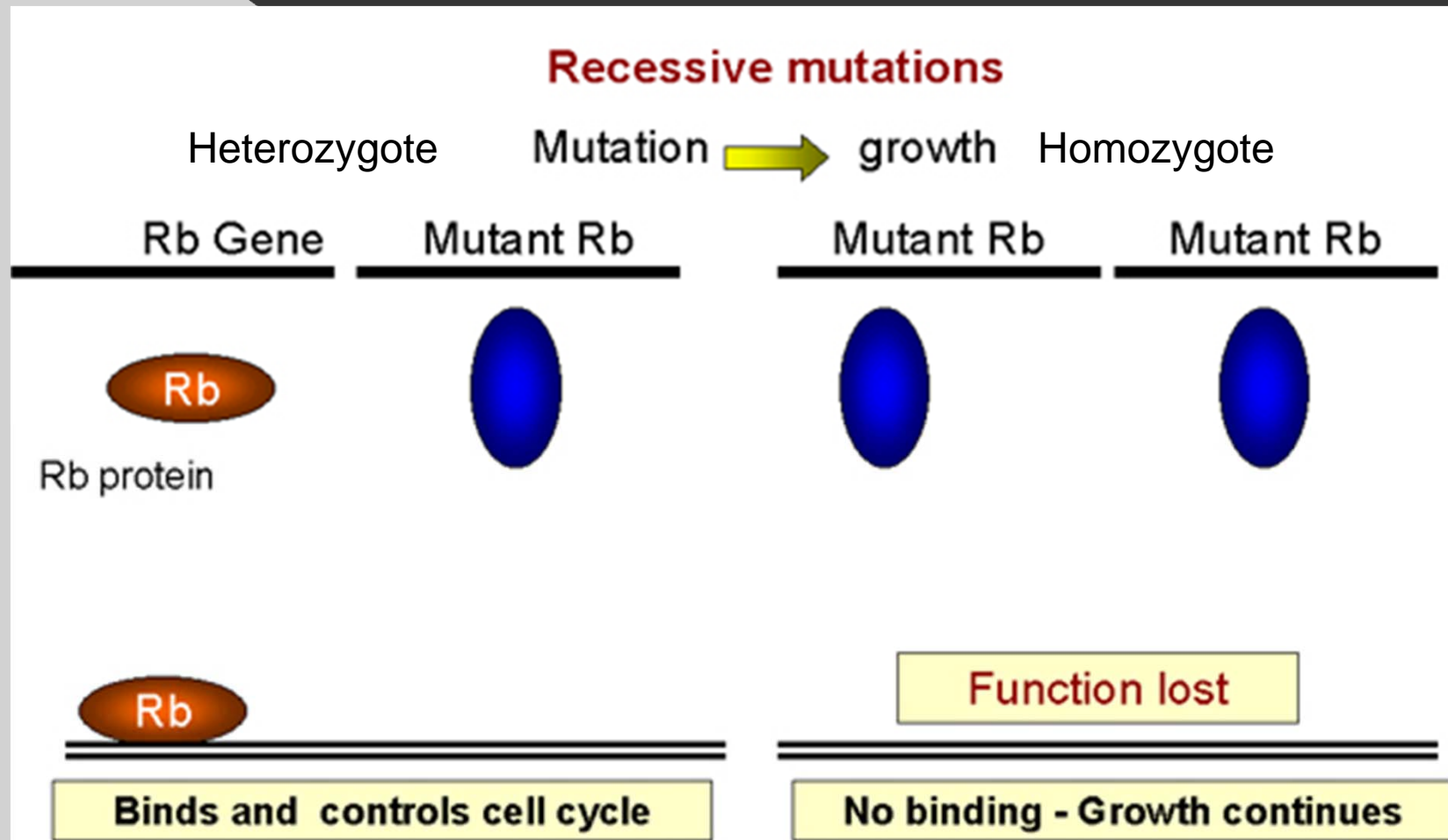
3. Alter expression of proto-oncogenes (c-oncs)

- ⊙ Normal cellular genes
 - > growth factors
 - > Receptor of growth factors
- ⊙ Sequence homologous to v-oncs
 - > Related to evolution and subsequently alter the gene
- ⊙ Several mechanisms convert c-oncs to oncogenes

Mutation of proto-oncogenes



Mutation of tumor-suppressor genes

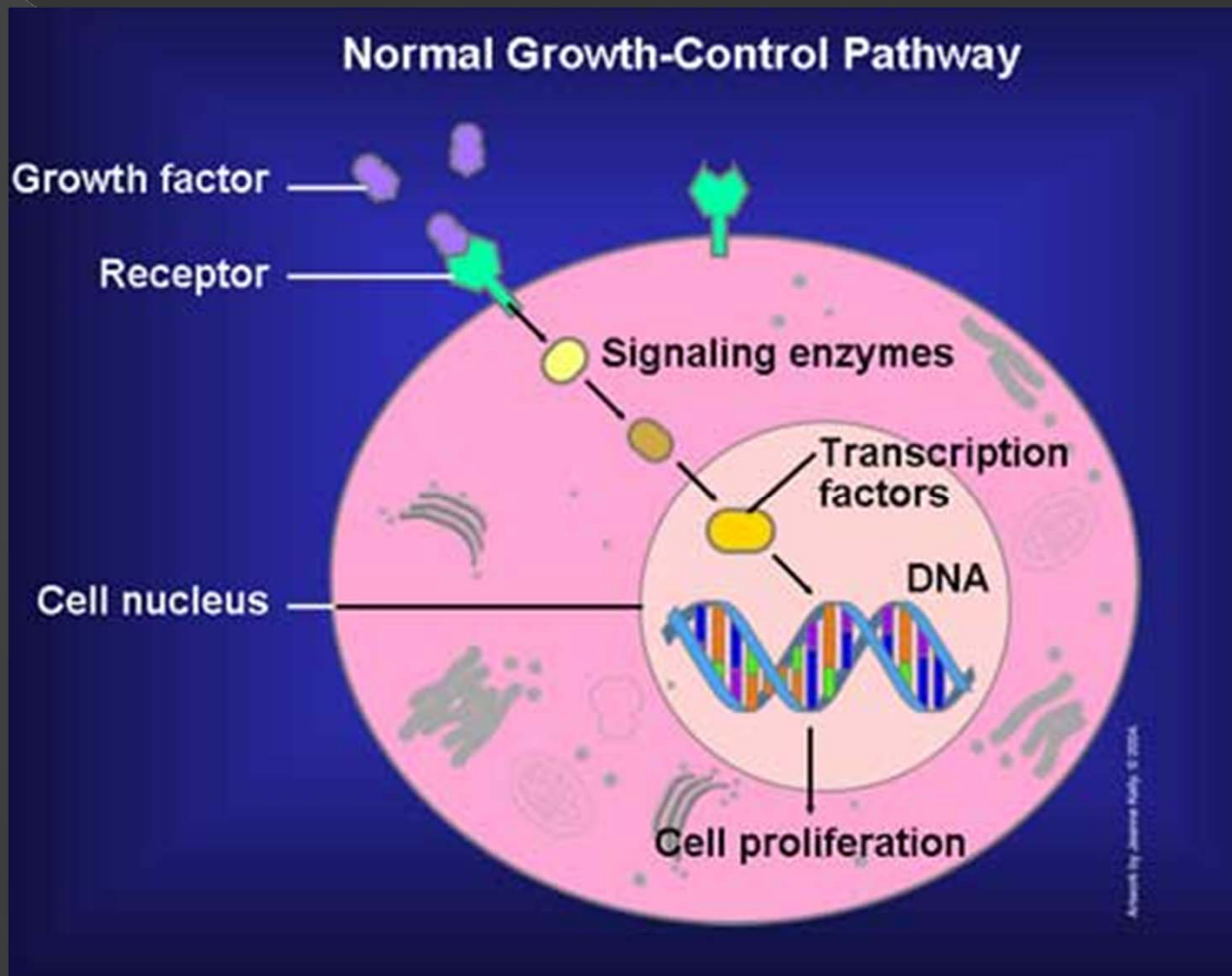


Mechanisms of Viral transformation

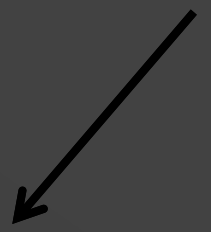
No single mechanism by which viruses cause tumor

- A. Perturbation of signaling pathway
- B. Deregulation of cell cycle
- C. Escape of apoptosis
- D. Immortalization of cells

A. Signaling pathway



Genetic perturbation of signaling pathway



Mimic the
cell surface ligands

HPV E5 encode
growth factor analog



Mimic the cellular
signaling receptors

EBV LMP1 protein
partially replace
CD40 in vivo



Mimic the intracellular
signaling adaptors

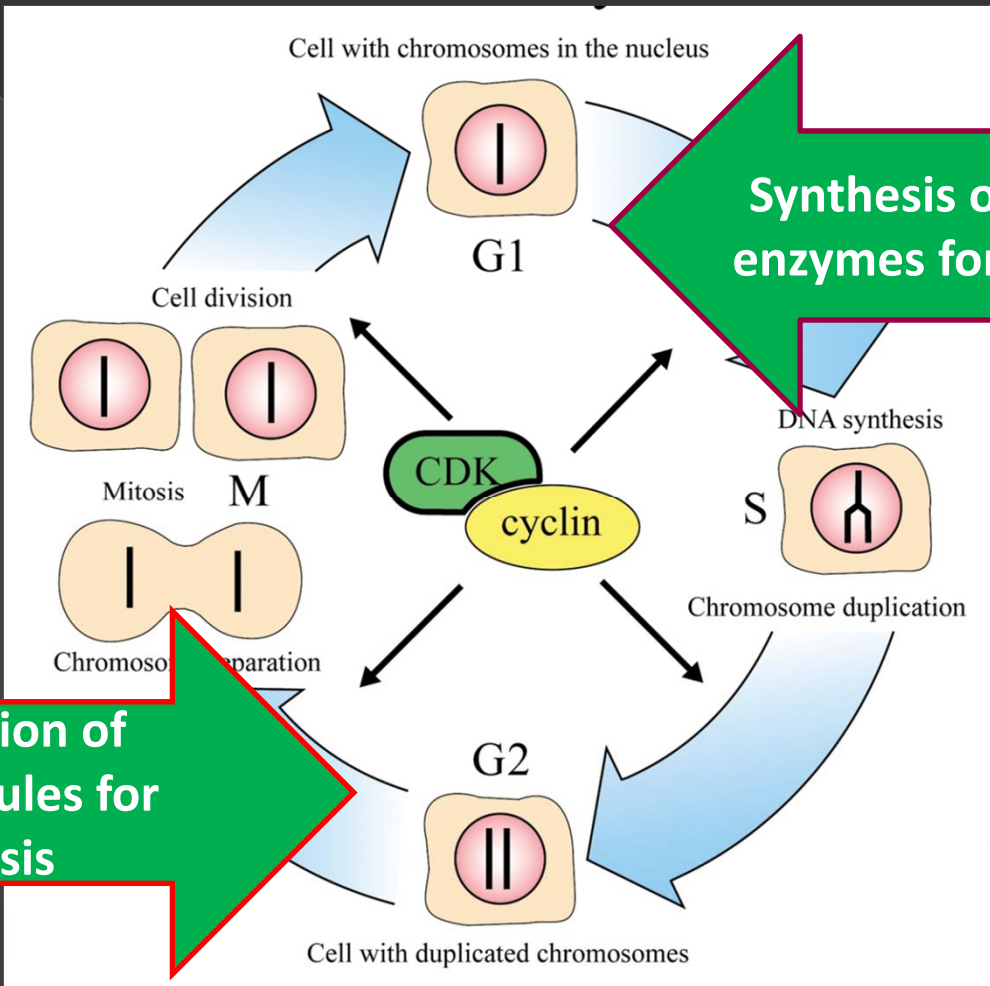
KSHV encode
viral FLICE
inhibitory
protein



Activate cell surface
receptors

HPV E5
stimulate
dimerization
& activation
of growth
factor

Phases of Cell Cycle



Synthesis of various enzymes for S phases

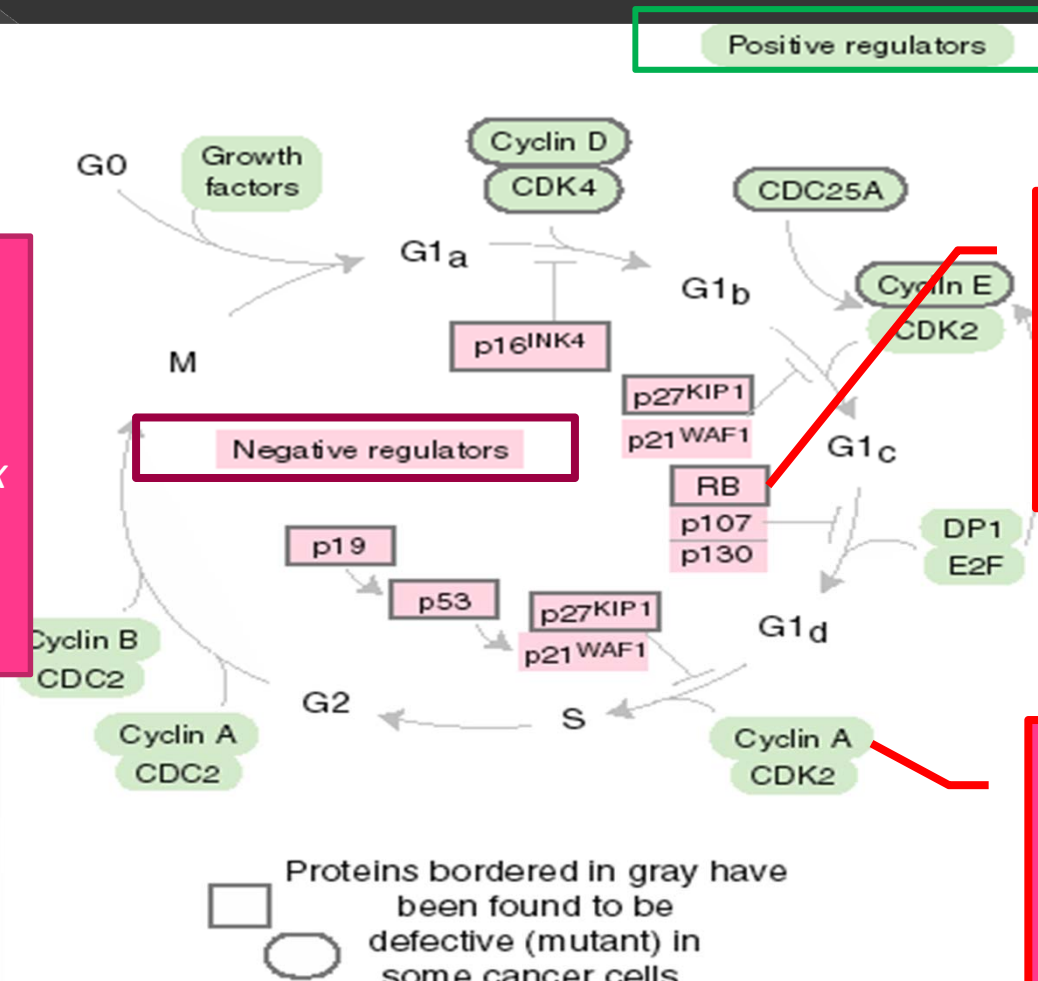
Production of microtubules for mitosis

Cell cycle and their control proteins

CDK

S

& HTLV-1 tax
bind to CDK



Abrogate RB function

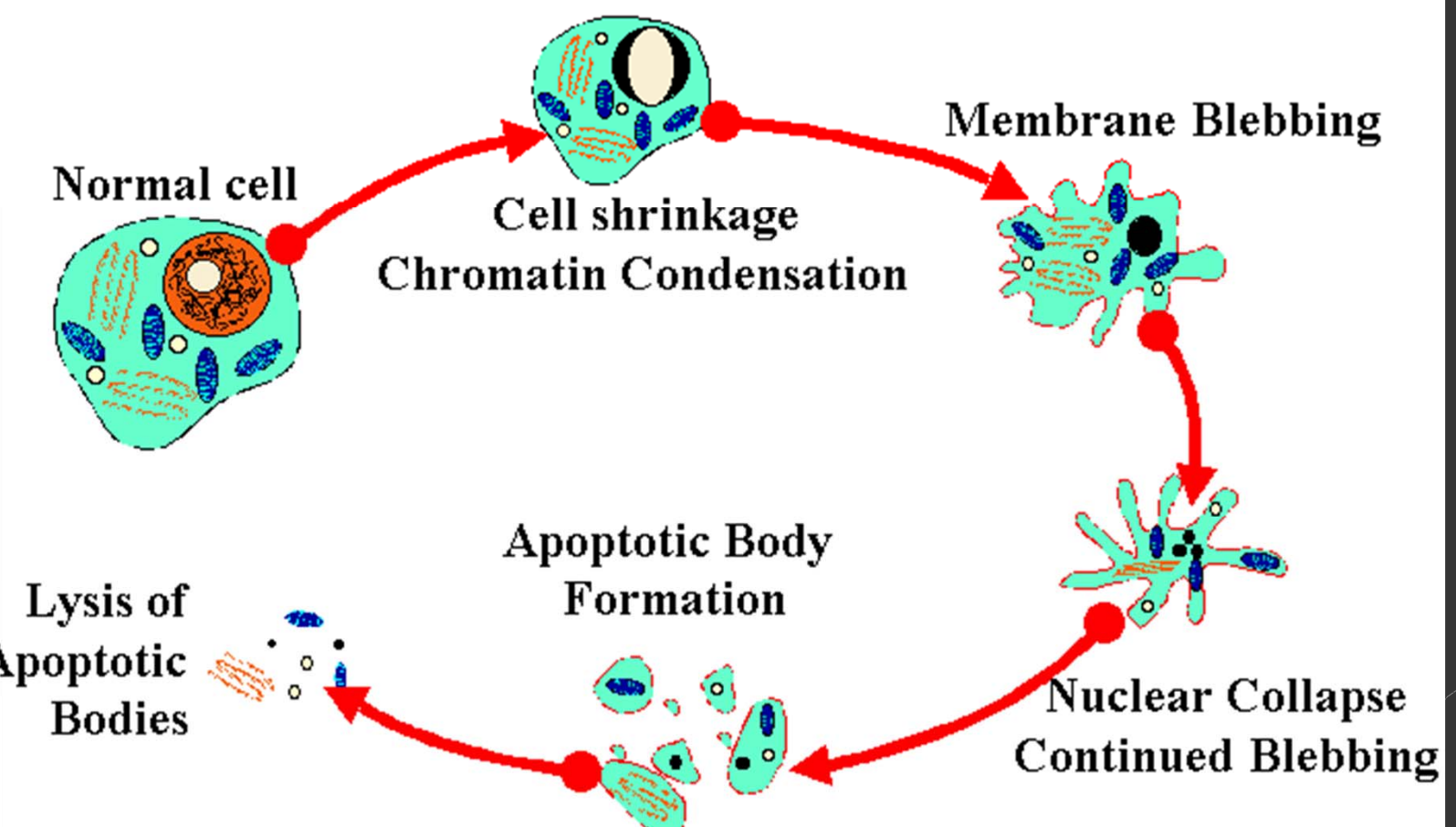
HPV E7protein

Targeting of cyclin

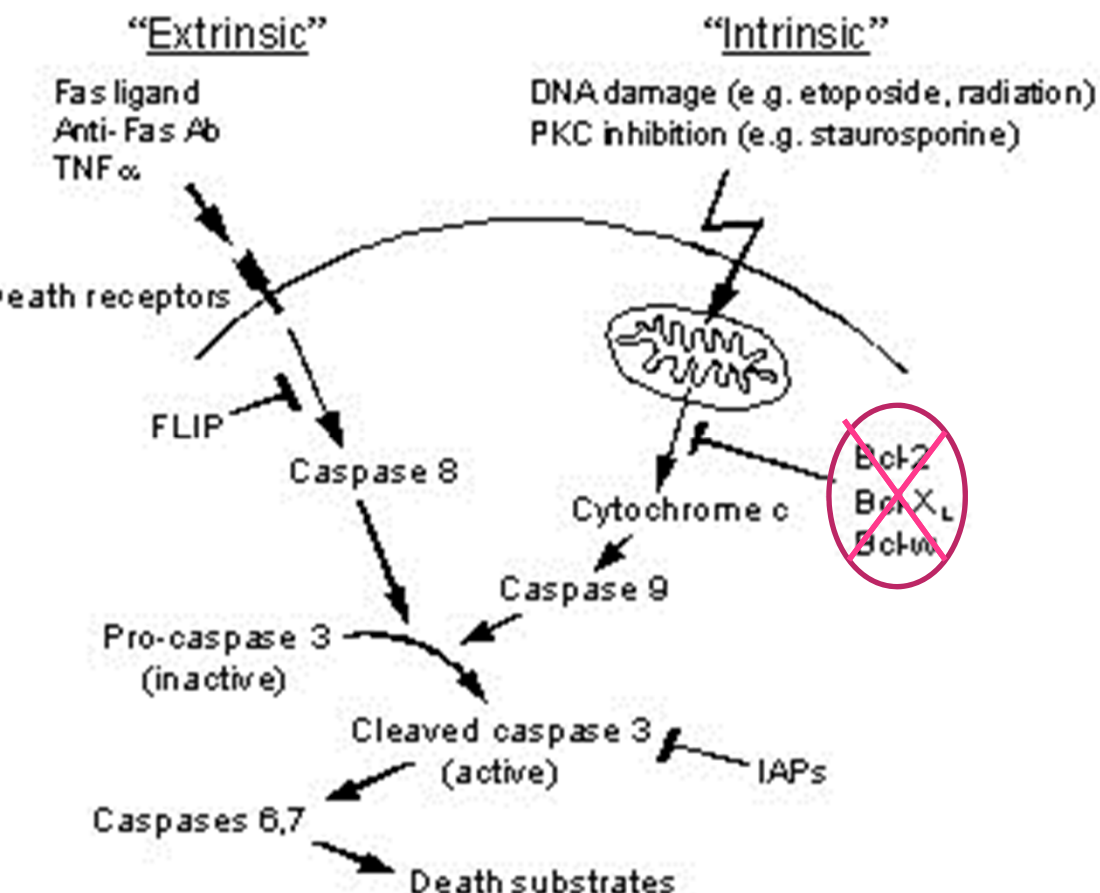
HTLV-1 tax protein
encode viral cyclin to
promote G1/S

C. General features of apoptosis

(Programmed Cell Death)



Escape of apoptosis



HPV E6 protein promote degradation of p53

P53 block Anti-apoptotic protein upon stress signal

EBV & KSHV encode viral Bc1-2 mimic action of cell Bc1-2

Role played by Telomere

60-70 cell division

Telomere: array of thousands of copies of a hexanucleotide repeat

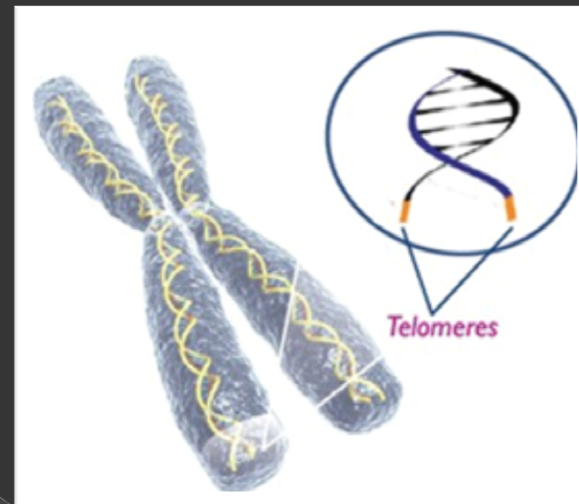
Shorten by 50-100 bp/cell division

2 enzymes restore length of telomere

TERC (telomerase RNA component)

TERT (telomerase reverse transcriptase)

High TERT activity in stem cells, cancer cells (>85%)



Cell immortalization

hTERT core promoter

NFX1

E GC

Normal somatic cells

E6AP
E6

NFX1

E GC

Cancer cells

ubiquitination

Examples of Tumor-inducing viruses

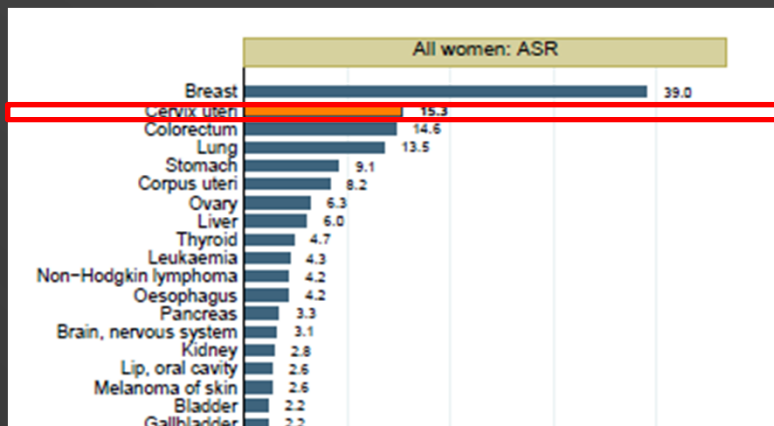
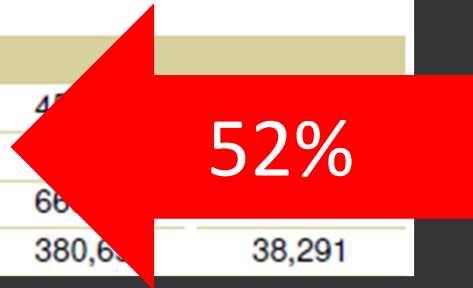
Oncovirus	Cancers
Epstein-Barr virus	Burkitt's lymphoma Nasopharyngeal carcinoma
Hepatitis B virus	Hepatocellular carcinoma
Hepatitis C virus	Hepatocellular carcinoma
Human papillomavirus	Cervical, oral and anogenital cancer
Human T-cell lymphotropic virus 1	Adult T-cell leukaemia
Kaposi sarcoma associated herpesvirus	Kaposi sarcoma, 1° effusion lymphoma

3. Cervical Cancer

Cervical Cancer Statistics

Table 1: Key statistics in the World

Population	World	Developing regions	Developed regions
Population at risk for cervical cancer (Female population aged >=15 yrs) in thousands	2,336,986	1,811,867	525,120
Incidence of Cervical cancer			
Total number of new cases of cervical cancer	529,828	470,000	59,828
Total number of cervical cancer deaths	275,128	240,000	35,128
Projected number of new cervical cancer cases in 2025*	720,060	660,000	60,060
Projected number of cervical cancer deaths in 2025*	395,095	380,000	15,095



Association of cervical cancer & carcinogenic HPVs

HPV causes virtually 100% of cases of cervical cancer necessary but not a sole factor

Papillomaviridae : about 200 types discovered

45 types anogenital

> About 17 Carcinogenic types

Majority: HPV 16 & 18

	Proportion of cervical cancers caused	Cumulative total cancers
HPV16	54.6%	54.6%
HPV18	15.8%	70.4%
HPV33	4.4%	74.8%
HPV45	3.7%	78.5%
HPV31	3.5%	82.0%
HPV58	3.4%	85.4%
HPV52	2.5%	87.9%
HPV35	1.8%	89.7%
HPV59	1.1%	90.8%
HPV56	0.8%	92.2%
HPV51	0.7%	92.9%
HPV39	0.7%	93.6%
HPV73	0.5%	94.1%
HPV68	0.5%	94.6%
HPV82	0.2%	94.8%
No type identified	5.2%	100%

HPV acquisition

Skin-to-skin or mucosa-to-mucosa

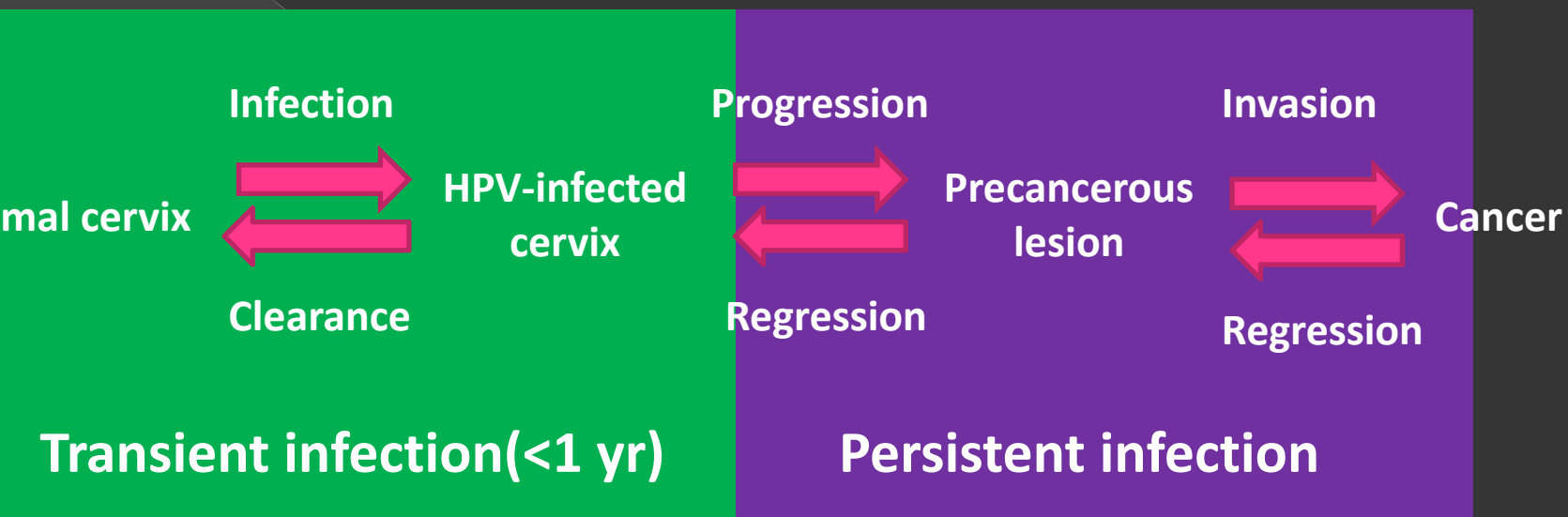
Horizontal transmission

- > Sexual intercourse
- > Nonpenetrative sexual contact
- > Contact with fomites

Vertical transmission (mother-to-child)

- > Give birth
- > Breast-feeding (possible)

Steps in Progression to Cervical cancer





Clinical Signs and Symptoms

Early : Asymptomatic

Progress: irregular vaginal bleeding

- > Postcoital, intermenstrual or postmenopausal
- > foul smell

Metastasis: various symptoms over the body

- > pelvic pain, backache
- > leg swelling
- > general malaise 抑鬱 and weight loss

Major prevention strategy: Vaccine

● 2 prophylactic vaccine



Quadrivalent vaccine

HPV 6, 11 (anogenital wart)
HPV 16, 18



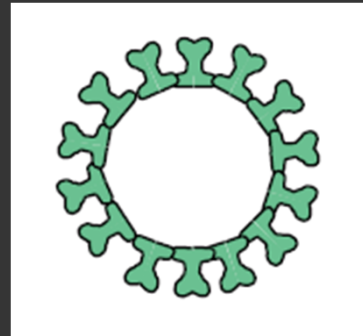
Bivalent vaccine

HPV 16, 18

Vaccine Composition & Safety

Subunit Vaccine

- > Purified L1 protein
- > Virus-like particles (VLPs)
 - More conformationally authentic
- > No viral genetic materials
 - Non-infectious



WHO Global Advisory Committee on Vaccine Safety

- > Well-tolerated
- > good safety profiles
- > No adverse reproductive outcome



Thank You

The image features a stylized graphic on a dark grey background. A light blue, tilted rectangular shape serves as a backdrop for the text. The word "Thank" is written in a bold, purple, sans-serif font, while "You" is written in a bold, orange, sans-serif font. A hand, rendered in a light orange color, is positioned over the word "You", making an "L" gesture with the index and thumb fingers. Three small, bright green, triangular shapes radiate from the top of the hand, suggesting motion or emphasis. The overall style is modern and graphic.